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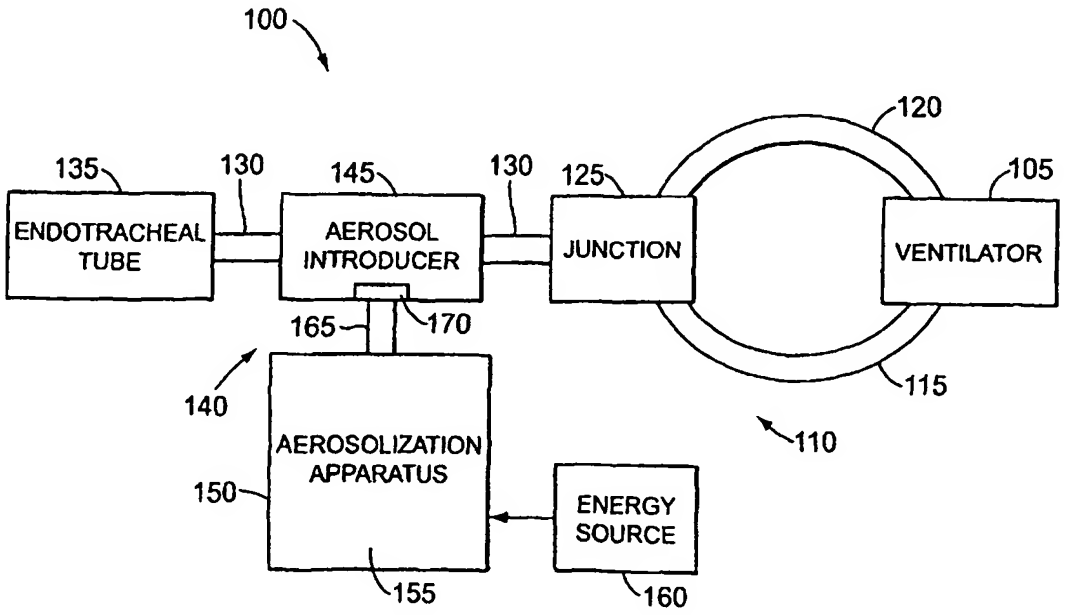
(54) Title: PHARMACEUTICAL DRY POWDER FORMULATION ON THE BASIS PARTICLES COMPRISING MULTIPLE ACTIVE AGENTS



(57) Abstract: One or more embodiments of the present invention relate to a pharmaceutical formulation on the basis of particles comprising multiple active agents.

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PHARMACEUTICAL DRY POWDER FORMULATION ON THE BASIS PARTICLES COMPRISING MULTIPLE ACTIVE AGENTS

Background of the Invention

[0001] One or more embodiments of the present invention relates to a pharmaceutical formulation comprising multiple active agents.

[0002] The need for effective therapeutic treatment of patients has resulted in the development of a variety of pharmaceutical formulation delivery techniques. One traditional technique involves the oral delivery of a pharmaceutical formulation in the form of a pill, capsule, elixir, or the like. However, oral delivery can in some cases be undesirable. For example, many pharmaceutical formulations may be degraded in the digestive tract before they can be effectively absorbed by the body. Inhaleable drug delivery, where an aerosolized pharmaceutical formulation is orally or nasally inhaled by a patient to deliver the formulation to the patient's respiratory tract, has proven to be a particularly effective and/or desirable alternative. For example, in one inhalation technique, an aerosolized pharmaceutical formulation provides local therapeutic relief to a portion of the respiratory tract, such as the lungs, to treat diseases such as asthma and emphysema. In another inhalation technique, a pharmaceutical formulation is delivered deep within a patient's lungs where it may be absorbed into the blood stream. Many types of aerosolization devices exist including devices comprising a pharmaceutical formulation stored in or with a propellant, devices that aerosolize a dry powder, devices which use a compressed gas to aerosolize a liquid pharmaceutical formulation, and similar devices.

[0003] One conventional type of aerosolization device is commonly referred to as a nebulizer. A nebulizer comprises a container having a reservoir which contains a liquid pharmaceutical formulation. The liquid pharmaceutical formulation generally comprises an active agent that is either in solution or suspended within the liquid. Energy is introduced into the reservoir to aerosolize the liquid pharmaceutical formulation so that it may be delivered to the lungs of a user. In one type of nebulizer, generally referred to as a jet nebulizer, compressed gas is forced through an orifice in the container. The compressed air forces liquid to be withdrawn through a nozzle, and the withdrawn liquid mixes with the flowing gas to form aerosol droplets. A cloud of the droplets is then administered to the user's respiratory tract. In another type of

nebulizer, generally referred to as an ultrasonic nebulizer, ultrasonic waves are generated to create high energy waves in the reservoir. These high energy waves aerosolize the liquid pharmaceutical formulation to create an aerosol cloud that is administered to the user's lungs. Nebulizers are particularly useful in delivering an aerosolized pharmaceutical formulation to a hospitalized or non-ambulatory patient; in delivering large doses of aerosolized active agent; and/or when delivering an aerosolized pharmaceutical formulation to a child or other patient unable to receive a dry powder or propellant based pharmaceutical formulation.

[0004] Nebulizers are particularly useful for delivering an aerosolized pharmaceutical formulation to the respiratory tract of a patient who is breathing under the assistance of a ventilator. However, there are problems associated with the introduction of the aerosolized pharmaceutical formulation into the ventilator circuit. For example, some formulations can be difficult to formulate into a liquid. In addition, it can be difficult and time consuming for healthcare workers to administer more than one active agent by nebulization.

[0005] Therefore, it is desirable to provide a way to introduce an aerosolized pharmaceutical formulation to a ventilated patient in a formulation that can be produced on a commercial scale. It is further desirable to provide a pharmaceutical formulation that is easily administratable.

Summary of the Invention

[0006] One or more embodiments of the present invention satisfies the above-described needs. In accordance with one embodiment of the present invention, a spray dried powder comprises two or more antibiotics. The dry powder may be administered as a dry powder or may be reconstituted for administration by injection or by nebulization.

Brief Description of the Drawings

[0007] Figure 1 is a schematic sectional view of an aerosolized pharmaceutical formulation delivery system according to one embodiment of the present invention;

[0008] Figures 2A and 2B are schematic sectional side views of a version of an aerosol introducer according to one embodiment of the present invention;

[0009] Figures 3A through 3C are schematic sectional side views of versions of an aerosol introducer;

[0010] Figures 4A through 4D are schematic sectional side views of other versions of an aerosol introducer;

[0011] Figures 5A through 5C are schematic sectional side views of other versions of an aerosol introducer;

[0012] Figures 6A through 6C are schematic sectional side views of other versions of an aerosol introducer;

[0013] Figure 7 is a schematic sectional side view of another version of an aerosol introducer; and

[0014] Figure 8 is a schematic sectional side view of an aerosol introducer being used as a nebulizer mouthpiece.

Detailed Description

[0015] One or more embodiments of the present invention relates to a pharmaceutical formulation comprising multiple active components. In particular, one or more embodiments of the present invention relates to an aerosolizable pharmaceutical formulation for administration to a patient on a ventilator. Although embodiments of the present invention are illustrated in the context of a liquid pharmaceutical formulation for a nebulizer, embodiments of the present invention can be used in other processes and should not be limited to the examples provided herein.

[0016] An aerosolized pharmaceutical formulation delivery system 100 according to one embodiment of the present invention is shown in Figure 1. The aerosolized pharmaceutical formulation delivery system 100 delivers an aerosolized pharmaceutical formulation to a portion of a user's respiratory tract, such as to the user's lungs. The aerosolized pharmaceutical formulation delivery system 100 is particularly useful in delivering the aerosolized pharmaceutical formulation to a patient whose breathing is being assisted by a ventilator 105. The ventilator circuit 110 is shown diagrammatically in Figure 1. As shown in Figure 1, an inhalation line 115 and an exhalation line 120 extend from the ventilator 105. The inhalation line 115 and the exhalation line 120 each are composed of tubing having an airflow lumen extending therethrough. The inhalation line 115 and the exhalation line 120 meet at a junction 125 remote from the ventilator 105. At the junction 125 the lumen of the inhalation

line 115 is in communication with the lumen from the exhalation line 120, and both of the aforementioned lumen are in communication with a patient line 130. The patient line 130 comprises a lumen that extends to the lumen of an endotracheal tube 135 which is inserted into the mouth of a patient. The endotracheal tube 135 has an opposite end that extends into or near the lungs of the user. Accordingly, in use, oxygenated air is introduced into the inhalation line 115 by the ventilator 105. The oxygenated air passes through the lumen of the inhalation line 115, into the patient line 130, through the lumen of the endotracheal tube 135, and into the lungs of the patient. The patient then exhales, either naturally or by applying negative pressure from the ventilator, and the exhaled air passes through the endotracheal tube 135, through the patient line 130, and through the exhalation line 120 to the ventilator 105. The cycle is continuously repeated to assist the patient's breathing or to entirely control the breathing of the patient.

[0017] The aerosolized pharmaceutical formulation delivery system 100 further comprises an aerosol introduction mechanism 140. The aerosol introduction mechanism 140 comprises an aerosol introducer 145 that introduces aerosolized pharmaceutical formulation into the ventilator circuit 110 at a position between the junction 125 and the lungs of the patient. For example, the aerosol introducer may introduce the aerosolized pharmaceutical formulation into the patient line 130, as shown in Figure 1, or may introduce the aerosolized pharmaceutical formulation within or near the endotracheal tube 135. The aerosol that is introduced by the aerosol introducer 145 is generated by an aerosolization apparatus 150 which comprises a reservoir for containing a pharmaceutical formulation. Aerosolization energy is supplied to the aerosolization device by an energy source 160 to generate the aerosolized pharmaceutical formulation. The aerosolized pharmaceutical formulation passes through a passage 165 to the aerosol introducer 145 where it may be introduced into the ventilator circuit 110. The aerosolization apparatus 150 may be, for example, a jet nebulizer where the energy source is compressed air, an ultrasonic nebulizer where the energy source is ultrasonic vibration, a metered does inhaler where the energy source is a boiling propellant, or a dry powder inhaler where the energy source is compressed or flowing air or is a vibrating membrane or the like.

[0018] An example of an aerosol introducer 145 for introducing the aerosolized

pharmaceutical formulation at a position between the junction 125 and the lungs of the patient is described in Gerald Smaldone et al's PCT Patent Application entitled "Methods, Devices and Formulations for Targeted Endobronchial Therapy", Medlen & Carroll Docket Number STONYB 8013, filed on May 7, 2003; in Gerald Smaldone et al's U.S. Patent Application 10/430,765, filed on May 6, 2003; in Gerald Smaldone et al's U.S. Patent Application 10/430,658, filed on May 6, 2003; and in U.S. Provisional Patent Applications 60/378,475; 60/380,783; 60/420,429; 60/439,894; and 60/442,785, all of which are incorporated herein by reference in their entireties.

[0019] The introduction of the aerosolized pharmaceutical formulation at a position between the junction 125 and the lungs of the patient is advantageous in many respects over the prior art systems where the aerosol is introduced into the inhalation line 115 near the junction 125 or within the ventilator 105. For example, by introducing the aerosolized pharmaceutical formulation at a position between the junction 125 and the lungs of the patient, the ventilator circuit volume from the point of introduction to the patient's lungs is substantially reduced. Accordingly, the aerosolized pharmaceutical formulation is more concentrated and is less diffused throughout the ventilator circuit 110. In addition, by residing in the inhalation line 115, much of the prior art aerosolized pharmaceutical formulation is drawn into the exhalation line 120, further limiting the efficiency of the administration. Because of this diffusion and this reduced efficiency, the consistency of dosing is difficult to control with the prior art systems. Also, the presence of high quantities of the aerosolized pharmaceutical formulation that are not administered to the lungs of the patient may be undesirable in that much of the aerosol may be introduced into the environment where it may be inhaled by healthcare workers or others.

[0020] While the introduction of the pharmaceutical formulation at a position between the junction 125 and the lungs of the patient is advantageous over the state of the art systems, as discussed above, it has been discovered that much of the introduced aerosolized pharmaceutical formulation may still be drawn into the exhalation line 120 prior to be administered to the patient. Therefore, the aerosol introducer 145 according to the invention has been designed to introduced the aerosolized pharmaceutical formulation in an improved manner to increase the efficiency and/or the consistency of the dosing. Accordingly, the aerosol introducer 145 introduces the aerosolized

pharmaceutical formulation into the inhalation flow at a position between the junction 125 and the lungs of the patient. In this way, the aerosol introducer 145 serves to reduce the amount of aerosolized pharmaceutical formulation that is drawn into the exhalation line 120 of the ventilator circuit 120.

[0021] In one version, the aerosol introducer 145 comprises a valving mechanism 170 to control the introduction of the aerosolized pharmaceutical formulation. For example, the valving mechanism 170 may comprise one or more valves that prevent or reduce the introduction of the aerosolized pharmaceutical formulation into the patient line 130 during the exhalation phase of the ventilator cycle and/or that prevent or reduce aerosolized pharmaceutical formulation present in the patient line 130 from being drawn out of the patient line 130 during the exhalation phase of the ventilator cycle.

[0022] A version of an aerosol introducer 145 which prevents or reduces the introduction of aerosolized pharmaceutical formulation into the patient line 130 is shown in Figures 2A and 2B. In this version, the aerosol introducer 145 comprises a body 175 that defines a lumen 180 which makes up at least a portion of the patient line 130. The body 175 of the aerosol introducer 145 has an extension portion 185 that is in communication with the aerosolization apparatus 150 and is able to receive aerosolized pharmaceutical formulation 190. Within the extension portion 185 a selectively openable valve 195 is positioned. The valve 195 is in a closed position during exhalation 200, as shown in Figure 2A, and is then in an open position during inhalation 205, as shown in Figure 2B.

[0023] Examples of the aerosol introducer 145 according to the version of Figures 2A and 2B are shown in Figures 3A through 3C. In the version shown in Figure 3A, a detector 210, such as a flow sensor, is positioned in the patient line 130 or elsewhere in the system to detect the occurrence of the inhalation phase or the exhalation phase. The detector 210 transmits a signal to a controller 215, such as a microprocessor or ASICs, which then generates a control signal in response to the detector signal to control the operation of the valve 195. Thus, when a signal from the detector 210 is determined to be indicative of an inhalation phase, the controller 215 causes the valve 195 to be in an open state, and when an exhalation phase is detected, the controller 215 causes the valve 195 to be in a closed state. In the versions of

Figures 3B and 3C, the valve 195 is a mechanical valve that operates in response to the flow of air in the lumen 180. In the version of Figure 3B, a L-shaped member 220 comprises a covering portion 225 that covers the extension portion 185 in the closed position to prevent the flow of aerosolized pharmaceutical formulation into the lumen 180. During inhalation, the flow of air contacts a protrusion 230 on the L-shaped member 220 which causes the L-shaped member 220 to pivot about a hinge 235 thereby lifting the covering portion at a position between the junction 125 and the lungs of the patient 225 and allowing the aerosolized pharmaceutical formulation to be introduced into the lumen 180. In the version of Figure 3, a compressible member 240 comprises a protrusion 245 that is acted on by the flowing air in the lumen 180. During inhalation, the flowing air causes the compressible member 240 to compress, for example by compressing an accordion section 250, thereby opening the extension portion 185, and during exhalation, the air flow cause the compressible member 240 to extend to the position shown in Figure 3C to close the extension portion 185 and prevent or reduce the flow of aerosolized pharmaceutical formulation into the lumen 180.

[0024] In another version, the lumen 180 of the aerosol introducer 145 is configured to prevent or reduce aerosolized pharmaceutical formulation present in the patient line 130 from being drawn out of the patient line 130 during the exhalation phase of the ventilator cycle. For example, as shown in Figure 4A, in one version, a wall 255 may be provided in the lumen 180 to divide the lumen into multiple channels, such as a first channel 260 and a second channel 265. The second channel 265 is in communication with the extension portion 185 so as to receive the aerosolized pharmaceutical formulation. In the version of Figure 4A, a one-way valve 270 is positioned in the second channel 265 so that only inhalation flow may pass through the second channel. Accordingly, only when inhalation air is flowing passed the extension portion 185 will aerosolized pharmaceutical formulation be drawn out of the aerosolization apparatus and delivered to the endotracheal tube and the patient. During exhalation, there is no flow through second channel 265, and aerosolized pharmaceutical formulation from the aerosolization apparatus is not withdrawn and excess aerosolized pharmaceutical formulation in the extension portion 185 and in the second channel 265 is not forced into the exhalation line 120.

[0025] Other versions of an aerosol introducer 145 having multiple channels are shown in Figures 4B through 4D. In the version of Figure 4B, a one-way valve 275 is positioned within the extension portion 185. In one version, the one-way valve 275 opens when air is flowing in the second channel 265. Since only inhalation flow is permitted in the second channel 265, as discussed above, the one-way valve 275 is only open during the inhalation phase. In the version of Figure 4C, a second one-way valve 280 is placed in the second channel 265 on the opposite side of the extension portion 185 from the first one-way valve 270. This valve prevents aerosolized pharmaceutical formulation within the second channel 265 from being driven back into the aerosolization apparatus and prevents any aerosolized pharmaceutical formulation in the second channel 265 from being drawn into the exhalation air flow in the first channel 260. In the version of Figure 4D, an oppositely directed one-way valve 290 is positioned in the first channel 260. In this version, only exhalation flow passes through the first channel 260. Accordingly, all of the inhalation flow passes through the second channel 265. In other version, the aerosol introducer includes a combination of any of the features shown in Figures 4A through 4D. Also, the cross-sectional dimensions of the channels may be adjusted and/or may vary relative to one another and/or may vary relative to the other dimensions within the patient line 130 to allow for desired flow characteristics in the system.

[0026] The aerosol introducer 145 may be configured for simple installation into a convention ventilator circuit 110. For example, as shown in Figure 5A, the aerosol introducer 145 may comprise an adapter having a first end 295 that is adapted to be connected to a conventional Y-piece serving as the junction 125. The aerosol introducer 145 of this version also comprises a second end 296 that is adapted to be connected to an end 310 of a conventional endotracheal tube 135. The extension portion 185 in this version is adapted to be connected to an output end of an aerosolization apparatus 150. Figure 5B shows another version of an aerosol introducer 154. This version is similar to the version of Figure 5A and further comprises a flexible portion 315 which allows the aerosol introducer to be placed a distance from the mouth of the patient. Figure 5C shows another version similar to the versions of Figures 5A and 5B, but with the aerosolization apparatus 150 and the aerosol introducer being integrated and/or being formed of a single piece.

[0027] In the version of Figures 5A, 5B, and 5C, the aerosol introducer 145 is in accordance with the version described in Figure 4A. However, any of the aforementioned versions may be substituted for the versions shown. When using the versions of Figures 5A through 5C, a healthcare worker disconnects the Y-piece 300 from the endotracheal tube 135 and inserts the aerosol introducer 145 between the two parts.

[0028] Another version of an aerosol introducer 145 is shown in Figures 6A through 6C. These versions are similar to the versions of Figures 5A through 5C, respectively, but with the Y-piece formed as an integral and/or single piece with the aerosol introducer 145. When using the versions of Figures 6A through 6C, a healthcare worker disconnects a Y-piece 300 from the endotracheal tube 135 and from the inhalation line 115 and the exhalation line 120. One of the aerosol introducers 145 of Figures 6A through 6C in then connected to the endotracheal tube 135 and to the inhalation line 115 and the exhalation line 120.

[0029] A specific version of an aerosol introducer 145 that is integrated into a Y-piece junction 125 is shown in Figure 7. This version is similar to the version of Figure 4D. In this version, the aerosol introducer 145 further comprises a swivel joint 315 which allows the orientation of the aerosolization apparatus 150 to be adjusted during use. Optionally, an HME filter may be provided in the second channel 260, for example at a position just before the one-way valve 290.

[0030] The aerosolization apparatus 150 may be of any type that is capable of producing respirable particles or droplets. For example, the pharmaceutical formulation may be in a dry powder form, as described for example in PCT publication WO 99/16419; in U.S. Patent 6,051,256, or in U.S. Patent 6,503,483, all of which are incorporated herein by reference in their entireties. In such cases, the aerosolization apparatus 150 may comprise an active dry powder aerosolization apparatus, such as a aerosolization apparatus described in U.S. Patent 5,485,135, U.S. Patent 5,740,794, U.S. Patent 6,257,233, all of which are incorporated herein by reference in their entireties, or a passive dry powder aerosolization apparatus, such as an aerosolization apparatus described in U.S. Patent 4,069,819 and in U.S. Patent 4,995,385, both of which are incorporated herein by reference in their entireties. Alternatively, the pharmaceutical formulation may comprise dissolved in or suspended in a liquid

propellant, as described in U.S. Patent 5,225,183; U.S. Patent 5,681,545; U.S. Patent 5,683,677; U.S. Patent 5,474,759; U.S. Patent 5,508,023; U.S. Patent 6,309,623 and in U.S. Patent 5,655,520 all of which are incorporated herein by reference in their entireties. In such cases, the aerosolization apparatus 150 may comprise a conventional metered dose inhaler (MDI). Alternatively, the pharmaceutical formulation may be in a liquid form and may be aerosolized using a conventional nebulizer as described in the aforementioned Gerald Smaldone et al's PCT Patent Application entitled "Methods, Devices and Formulations for Targeted Endobronchial Therapy", Medlen & Carroll Docket Number STONYB 8013, filed on May 7, 2003; in Gerald Smaldone et al's U.S. Patent Application 10/430,765, filed on May 6, 2003; in Gerald Smaldone et al's U.S. Patent Application 10/430,658, filed on May 6, 2003; and in U.S. Provisional Patent Applications 60/378,475; 60/380,783; 60/420,429; 60/439,894; and 60/442,785, all of which are incorporated herein by reference in their entireties. Other examples of suitable nebulizers include the Aerogen Pro or Aeroneb® Pro, available from Aerogen, Inc. in Mountain View, CA; the Lumiscope ® Nebulizer 6600 or 6610 available from the Lumiscope Company, Inc. in East Brunswick, NJ; and the Omron NE-U22 available from Omron Healthcare, Inc. in Kyoto, Japan.

[0031] It has been found that a nebulizer that forms droplets without the use of compressed gas, such as the Aerogen Pro or Aeroneb Pro, provides unexpected improvement in dosing efficiency and consistency. By generating fine droplets by using a vibrating perforated or unperforated membrane, rather than by introducing compressed air, the aerosolized pharmaceutical formulation can be introduced into the ventilator circuit 110 without substantially affecting the flow characteristics within the circuit and without requiring a substantial re-selection of the ventilator settings. In addition, the generated droplets when using a nebulizer of this type are introduced at a low velocity, thereby decreasing the likelihood of the droplets being driven to an undesired region of the ventilator circuit 110. Furthermore, the combination of a droplet forming nebulizer and an aerosol introducer 145 as described is beneficial in that there is a reduction in the variability of dosing when different tidal volumes are used by the ventilator, thus making the system more universal.

[0032] In another version, as shown in Figure 8, the aerosol introducer 145 may be used to administered aerosolized pharmaceutical formulation to patients other than

those on a ventilator. For example, the aerosol introducer 145 may be used as a mouthpiece 400 for a nebulizer. Accordingly, the aerosol introducer 145 may have one end 405 that is shaped to be received in a user's mouth or nose, and the aerosol introducer may have a second end 410 that is open to ambient air. Any of the above mentioned versions may be modified in this manner.

[0033] The pharmaceutical formulation may comprise an active agent for administration to the respiratory tract of the user. The active agent described herein includes an agent, drug, compound, composition of matter or mixture thereof which provides some pharmacologic, often beneficial, effect. This includes foods, food supplements, nutrients, drugs, vaccines, vitamins, and other beneficial agents. As used herein, the terms further include any physiologically or pharmacologically active substance that produces a localized or systemic effect in a patient. An active agent for incorporation in the pharmaceutical formulation described herein may be an inorganic or an organic compound, including, without limitation, drugs which act on: the peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synoptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autacoid systems, the alimentary and excretory systems, the histamine system, and the central nervous system.

[0034] In one particular embodiment, the pharmaceutical formulation comprises an antibiotic for administration to a ventilated patient to treat or prevent ventricular assisted pneumonia. Such administration is described in aforementioned Gerald Smaldone et al's PCT Patent Application entitled "Methods, Devices and Formulations for Targeted Endobronchial Therapy", Medlen & Carroll Docket Number STONYB 8013, filed on May 7, 2003; in Gerald Smaldone et al's U.S. Patent Application 10/430,765, filed on May 6, 2003; in Gerald Smaldone et al's U.S. Patent Application 10/430,658, filed on May 6, 2003; and in U.S. Provisional Patent Applications 60/378,475; 60/380,783; 60/420,429; 60/439,894; and 60/442,785, all of which are incorporated herein by reference in their entireties. Using an aerosol introducer 145 according to the present invention in connection with the administration of aerosolized antibiotics offers substantial benefits. For example, when using the aerosol introducer 145 of the invention, substantially less pharmaceutical formulation is lost to the

environment which results in a reduction in bacterial resistance against the antibiotic. In addition, the aerosol introducer 145 is able to deliver a more consistent dose which is particularly useful for antibiotic therapy.

[0035] The pharmaceutical formulation may be formulated by a process which allows the pharmaceutical formulation to be easily and effectively administered. For example, the pharmaceutical formulation may be formulated as a dry powder. The dry powder may be administered as a dry powder in a dry powder inhaler, may be introduced with propellant into an MDI canister, or may be reconstituted, such as by being added to water, for nebulization. Alternatively, the reconstituted dry powder could be administered by injection.

[0036] In one version, the dry powder may comprise multiple active agents. The use of multiple active agents simplifies the administration process for the user or for a healthcare worker. In addition, by co-formulating the active agents, the step of mixing different powders is avoided, thereby improving dose content uniformity. In addition, by selectively adjusting the composition of the dry powder, precipitation of one of the components in the reconstituted solution can be avoided. In one version, the dry powder may comprise two or more antibiotics. In one particular version, the dry powder comprises a first antibiotic selected to treat gram negative infections and a second antibiotic selected to treat gram positive antibiotics. Various gram negative and gram positive antibiotics are described in aforementioned Gerald Smaldone et al's PCT Patent Application entitled "Methods, Devices and Formulations for Targeted Endobronchial Therapy", Medlen & Carroll Docket Number STONYB 8013, filed on May 7, 2003; in Gerald Smaldone et al's U.S. Patent Application 10/430,765, filed on May 6, 2003; in Gerald Smaldone et al's U.S. Patent Application 10/430,658, filed on May 6, 2003; and in U.S. Provisional Patent Applications 60/378,475; 60/380,783; 60/420,429; 60/439,894; and 60/442,785, all of which are incorporated herein by reference in their entireties.

[0037] In one method of use, a dry powder comprising a gram negative antibiotic and a gram positive antibiotic is reconstituted in water and is administered by nebulization to a ventilated patient, as described above, to treat or prevent ventilator assisted pneumonia. In a particular method, the dry powder comprises vancomycin and gentamycin.

[0038] In one version, the dry powder may be formulated by spray drying a solution containing a gram negative antibiotic and a gram positive antibiotic. Alternatively, the spray dried solution may comprise only one of the antibiotics. Optionally, an excipient, such as trileucine or another flow enhancing agent, may be added to the solution to modify the surface properties and to improve the flowability of the resulting dry powder. The addition of trileucine is described in U.S. Patent 6,518,239 which is incorporated herein by reference in its entirety. Other flow enhancing excipients include other amino acids, di- and tri-peptides.

[0039] The amount of each antibiotic contained in the powder particles will be that amount necessary to pulmonarily deliver a therapeutically effective amount (i.e., bactericidal amount) of the antibiotic per unit dose over the course of a dosing regimen. In practice, this will vary depending upon the particular antibiotic, its MIC_{90} value against the target pathogen(s) (e.g., respiratory tract pathogens), the severity of the infection to be treated, the patient population, and dosing requirements. A notable advantage of the respirable compositions described herein is their ability to be delivered directly to the site of infection - the lung, rather than in the case of systemic antibiotic formulations, where only a small portion of the orally or intravenously delivered antibiotic reaches the lung tissue via the circulation. This allows for the administering of lower overall doses of antibiotic than are typically administered orally or intravenously.

[0040] Dry powder co-antibiotic formulations are preferably prepared by spray drying. Spray drying of the formulations is carried out, for example, as described generally in the "Spray Drying Handbook", 5th ed., K. Masters, John Wiley & Sons, Inc., NY, NY (1991), and in Platz, R., *et al.*, International Patent Publication No. WO 97/41833 (1997), all of which are incorporated herein by reference in their entireties.

[0041] To prepare a co-antibiotic solution for spray-drying, the antibiotics (and any other excipients) are generally dissolved in water, optionally containing a physiologically acceptable buffer. The pH range of antibiotic solutions is generally between about 3 and 10, with nearer neutral pHs being preferred, since such pHs may aid in maintaining the physiological compatibility of the powder after dissolution of powder within the lung. The aqueous formulation may optionally contain additional water-miscible solvents, such as acetone, alcohols and the like. Representative alcohols

are lower alcohols such as methanol, ethanol, propanol, isopropanol, and the like. The antibiotic solutions will generally contain antibiotic dissolved at a concentration from 0.01% (weight/volume) to about 20% (weight/volume), usually from 0.1% to 3% (weight/volume). Alternatively, the antibiotic may be spray-dried using an organic solvent or co-solvent system, employing one or more solvents such as acetone, alcohols (e.g., methanol and ethanol), ethers, aldehydes, hydrocarbons, ketones, and polar aprotic solvents.

[0042] The co-antibiotic containing solutions are then spray dried in a conventional spray drier, such as those available from commercial suppliers such as Niro A/S (Denmark), Buchi (Switzerland) and the like, resulting in a dispersible, co-antibiotic dry powder. Optimal conditions for spray drying the antibiotic solutions will vary depending upon the formulation components, and are generally determined experimentally. The gas used to spray dry the material is typically air, although inert gases such as nitrogen or argon are also suitable. Moreover, the temperature of both the inlet and outlet of the gas used to dry the sprayed material is such that it does not cause decomposition of the antibiotic in the sprayed material. Such temperatures are typically determined experimentally, although generally, the inlet temperature will range from about 50° C to about 200° C while the outlet temperature will range from about 30° C to about 150° C.

[0043] Alternatively, the co-antibiotic dry powders may be prepared by lyophilization, vacuum drying, spray freeze drying, super critical fluid processing, air drying, or other forms of evaporative drying. In some instances, it may be desirable to provide the co-antibiotic dry powder formulation in a form that possesses improved handling/processing characteristics, e.g., reduced static, better flowability, low caking, and the like, by preparing compositions composed of fine particle aggregates, that is, aggregates or agglomerates of the above-described antibiotic dry powder particles, where the aggregates are readily broken back down to the fine powder components for pulmonary delivery, as described, e.g., in Johnson, K., *et al.*, U.S. Patent No. 5,654,007, 1997, incorporated herein by reference. Alternatively, the co-antibiotic powders may be prepared by agglomerating the powder components, sieving the materials to obtain the agglomerates, spheronizing to provide a more spherical agglomerate, and sizing to obtain a uniformly-sized product, as described, e.g., and in

Ahlneck, C., *et al.*, International PCT Publication No. WO 95/09616, 1995, incorporated herein by reference. The co-antibiotic dry powders in accordance with one or more embodiments of the present invention may also be prepared by blending, grinding, sieving or jet milling formulation components in dry powder form. The antibiotic dry powders are preferably maintained under dry (*i.e.*, relatively low humidity) conditions during manufacture, processing, and storage. Irrespective of the drying process employed, the process will preferably result in respirable, highly dispersible particles composed of an antibiotic.

[0044] Alternatively or additionally, suitable active agents may be selected from, for example, hypnotics and sedatives, psychic energizers, tranquilizers, respiratory drugs, anticonvulsants, muscle relaxants, antiparkinson agents (dopamine antagnonists), analgesics, anti-inflammatories, antianxiety drugs (anxiolytics), appetite suppressants, antimigraine agents, muscle contractants, anti-infectives (antibiotics, antivirals, antifungals, vaccines) antiarthritics, antimalarials, antiemetics, anepileptics, bronchodilators, cytokines, growth factors, anti-cancer agents, antithrombotic agents, antihypertensives, cardiovascular drugs, antiarrhythmics, antioxicants, anti-asthma agents, hormonal agents including contraceptives, sympathomimetics, diuretics, lipid regulating agents, antiandrogenic agents, antiparasitics, anticoagulants, neoplastics, antineoplastics, hypoglycemics, nutritional agents and supplements, growth supplements, antienteritis agents, vaccines, antibodies, diagnostic agents, and contrasting agents. The active agent, when administered by inhalation, may act locally or systemically.

[0045] The active agent may fall into one of a number of structural classes, including but not limited to small molecules, peptides, polypeptides, proteins, polysaccharides, steroids, proteins capable of eliciting physiological effects, nucleotides, oligonucleotides, polynucleotides, fats, electrolytes, and the like.

[0046] Examples of active agents suitable for use in this invention include but are not limited to one or more of calcitonin, amphotericin B, erythropoietin (EPO), Factor VIII, Factor IX, ceredase, cerezyme, cyclosporin, granulocyte colony stimulating factor (GCSF), thrombopoietin (TPO), alpha-1 proteinase inhibitor, elcatonin, granulocyte macrophage colony stimulating factor (GMCSF), growth hormone, human growth hormone (HGH), growth hormone releasing hormone

(GHRH), heparin, low molecular weight heparin (LMWH), interferon alpha, interferon beta, interferon gamma, interleukin-1 receptor, interleukin-2, interleukin-1 receptor antagonist, interleukin-3, interleukin-4, interleukin-6, luteinizing hormone releasing hormone (LHRH), factor IX, insulin, pro-insulin, insulin analogues (e.g., mono-acylated insulin as described in U.S. Patent No. 5,922,675, which is incorporated herein by reference in its entirety), amylin, C-peptide, somatostatin, somatostatin analogs including octreotide, vasopressin, follicle stimulating hormone (FSH), insulin-like growth factor (IGF), insulintropin, macrophage colony stimulating factor (M-CSF), nerve growth factor (NGF), tissue growth factors, keratinocyte growth factor (KGF), glial growth factor (GGF), tumor necrosis factor (TNF), endothelial growth factors, parathyroid hormone (PTH), glucagon-like peptide thymosin alpha 1, IIb/IIIa inhibitor, alpha-1 antitrypsin, phosphodiesterase (PDE) compounds, VLA-4 inhibitors, bisphosponates, respiratory syncytial virus antibody, cystic fibrosis transmembrane regulator (CFTR) gene, deoxyreibonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, 13-cis retinoic acid, macrolides such as erythromycin, oleandomycin, troleandomycin, roxithromycin, clarithromycin, davercin, azithromycin, flurithromycin, dirithromycin, josamycin, spiromycin, midecamycin, leucomycin, miocamycin, rokitamycin, andazithromycin, and swinolide A; fluoroquinolones such as ciprofloxacin, ofloxacin, levofloxacin, trovafloxacin, alatrofloxacin, moxifloxicin, norfloxacin, enoxacin, grepafloxacin, gatifloxacin, lomefloxacin, sparfloxacin, temafloxacin, pefloxacin, amifloxacin, fleroxacin, tosufloxacin, prulifloxacin, irloxacin, pazufloxacin, clinafloxacin, and sitafloxacin, aminoglycosides such as gentamicin, netilmicin, paramecin, tobramycin, amikacin, kanamycin, neomycin, and streptomycin, vancomycin, teicoplanin, rampolanin, mideplanin, colistin, daptomycin, gramicidin, colistimethate, polymixins such as polymixin B, capreomycin, bacitracin, penems; penicillins including penicllinase-sensitive agents like penicillin G, penicillin V, penicillinase-resistant agents like methicillin, oxacillin, cloxacillin, dicloxacillin, floxacillin, nafcillin; gram negative microorganism active agents like ampicillin, amoxicillin, and hetacillin, cillin, and galampicillin; antipseudomonal penicillins like carbenicillin, ticarcillin, azlocillin, mezlocillin, and piperacillin; cephalosporins like cefpodoxime, cefprozil, ceftbuten, ceftizoxime, ceftriaxone, cephalothin, cephapirin, cephalexin, cephradrine, cefoxitin,

cefamandole, cefazolin, cephaloridine, cefaclor, cefadroxil, cephaloglycin, cefuroxime, ceforanide, cefotaxime, cefatrizine, cephacetrile, cefepime, cefixime, cefonicid, cefoperazone, cefotetan, cefmetazole, ceftazidime, loracarbef, and moxalactam, monobactams like aztreonam; and carbapenems such as imipenem, meropenem, pentamidine isethiouate, albuterol sulfate, lidocaine, metaproterenol sulfate, beclomethasone diprepionate, triamcinolone acetamide, budesonide acetonide, fluticasone, ipratropium bromide, flunisolide, cromolyn sodium, ergotamine tartrate and where applicable, analogues, agonists, antagonists, inhibitors, and pharmaceutically acceptable salt forms of the above. In reference to peptides and proteins, the invention is intended to encompass synthetic, native, glycosylated, unglycosylated, pegylated forms, and biologically active fragments and analogs thereof.

[0047] Active agents for use in the invention further include nucleic acids, as bare nucleic acid molecules, vectors, associated viral particles, plasmid DNA or RNA or other nucleic acid constructions of a type suitable for transfection or transformation of cells, i.e., suitable for gene therapy including antisense. Further, an active agent may comprise live attenuated or killed viruses suitable for use as vaccines. Other useful drugs include those listed within the Physician's Desk Reference (most recent edition).

[0048] The amount of these active agents in the pharmaceutical formulation will be that amount necessary to deliver a therapeutically effective amount of the active agent per unit dose to achieve the desired result. In practice, this will vary widely depending upon the particular agent, its activity, the severity of the condition to be treated, the patient population, dosing requirements, and the desired therapeutic effect. The composition will generally contain anywhere from about 1% by weight to about 99% by weight active agent, typically from about 2% to about 95% by weight active agent, and more typically from about 5% to 85% by weight active agent, and will also depend upon the relative amounts of additives contained in the composition. The compositions of the invention are particularly useful for active agents that are delivered in doses of from 0.001 mg/day to 100 mg/day, preferably in doses from 0.01 mg/day to 75 mg/day, and more preferably in doses from 0.10 mg/day to 50 mg/day. It is to be understood that more than one active agent may be incorporated into the formulations described herein and that the use of the term "agent" in no way excludes the use of two or more such agents.

[0049] The pharmaceutical formulation may comprise a pharmaceutically acceptable excipient or carrier which may be taken into the lungs with no significant adverse toxicological effects to the subject, and particularly to the lungs of the subject. In addition to the active agent, a pharmaceutical formulation may optionally include one or more pharmaceutical excipients which are suitable for pulmonary administration. These excipients, if present, are generally present in the composition in amounts ranging from about 0.01 % to about 95% percent by weight, preferably from about 0.5 to about 80%, and more preferably from about 1 to about 60% by weight. Preferably, such excipients will, in part, serve to further improve the features of the active agent composition, for example by providing more efficient and reproducible delivery of the active agent, improving the handling characteristics of powders, such as flowability and consistency, and/or facilitating manufacturing and filling of unit dosage forms. In particular, excipient materials can often function to further improve the physical and chemical stability of the active agent, minimize the residual moisture content and hinder moisture uptake, and to enhance particle size, degree of aggregation, particle surface properties, such as rugosity, ease of inhalation, and the targeting of particles to the lung. One or more excipients may also be provided to serve as bulking agents when it is desired to reduce the concentration of active agent in the formulation.

[0050] Pharmaceutical excipients and additives useful in the present pharmaceutical formulation include but are not limited to amino acids, peptides, proteins, non-biological polymers, biological polymers, carbohydrates, such as sugars, derivatized sugars such as alditols, aldonic acids, esterified sugars, and sugar polymers, which may be present singly or in combination. Suitable excipients are those provided in WO 96/32096, which is incorporated herein by reference in its entirety. The excipient may have a glass transition temperatures (Tg) above about 35° C, preferably above about 40 °C, more preferably above 45° C, most preferably above about 55 °C.

[0051] Exemplary protein excipients include albumins such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, hemoglobin, and the like. Suitable amino acids (outside of the dileucyl-peptides of the invention), which may also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, tyrosine, tryptophan, and the like. Preferred are

amino acids and polypeptides that function as dispersing agents. Amino acids falling into this category include hydrophobic amino acids such as leucine, valine, isoleucine, tryptophan, alanine, methionine, phenylalanine, tyrosine, histidine, and proline. Dispersibility-enhancing peptide excipients include dimers, trimers, tetramers, and pentamers comprising one or more hydrophobic amino acid components such as those described above.

[0052] Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), pyranosyl sorbitol, myoinositol and the like.

[0053] The pharmaceutical formulation may also include a buffer or a pH adjusting agent, typically a salt prepared from an organic acid or base. Representative buffers include organic acid salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid, Tris, tromethamine hydrochloride, or phosphate buffers.

[0054] The pharmaceutical formulation may also include polymeric excipients/additives, e.g., polyvinylpyrrolidones, derivatized celluloses such as hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylmethylcellulose, Ficolls (a polymeric sugar), hydroxyethylstarch, dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin), polyethylene glycols, and pectin.

[0055] The pharmaceutical formulation may further include flavoring agents, taste-masking agents, inorganic salts (for example sodium chloride), antimicrobial agents (for example benzalkonium chloride), sweeteners, antioxidants, antistatic agents, surfactants (for example polysorbates such as "TWEEN 20" and "TWEEN 80"), sorbitan esters, lipids (for example phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines), fatty acids and fatty esters, steroids (for example cholesterol), and chelating agents (for example EDTA, zinc and other such suitable cations). Other pharmaceutical excipients and/or additives suitable for use in the compositions according to the invention are listed in "Remington: The

Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), both of which are incorporated herein by reference in their entireties.

[0056] For MDI applications, the pharmaceutical formulation may also be treated so that it has high stability. Several attempts have dealt with improving suspension stability by increasing the solubility of surface-active agents in the HFA propellants. To this end U.S. Pat. No. 5,118,494, WO 91/11173 and WO 92/00107 disclose the use of HFA soluble fluorinated surfactants to improve suspension stability. Mixtures of HFA propellants with other perfluorinated cosolvents have also been disclosed as in WO 91/04011. Other attempts at stabilization involved the inclusion of nonfluorinated surfactants. In this respect, U.S. Pat. No. 5,492,688 discloses that some hydrophilic surfactants (with a hydrophilic/lipophilic balance greater than or equal to 9.6) have sufficient solubility in HFAs to stabilize medicament suspensions. Increases in the solubility of conventional nonfluorinated MDI surfactants (e.g. oleic acid, lecithin) can also reportedly be achieved with the use of co-solvents such as alcohols, as set forth in U.S. Pat. Nos. 5,683,677 and 5,605,674, as well as in WO 95/17195. Unfortunately, as with the prior art cosolvent systems previously discussed, merely increasing the repulsion between particles has not proved to be a very effective stabilizing mechanism in nonaqueous dispersions, such as MDI preparations. All of the aforementioned references being incorporated herein by reference in their entireties.

[0057] "Mass median diameter" or "MMD" is a measure of mean particle size, since the powders of the invention are generally polydisperse (i.e., consist of a range of particle sizes). MMD values as reported herein are determined by centrifugal sedimentation, although any number of commonly employed techniques can be used for measuring mean particle size. "Mass median aerodynamic diameter" or "MMAD" is a measure of the aerodynamic size of a dispersed particle. The aerodynamic diameter is used to describe an aerosolized powder in terms of its settling behavior, and is the diameter of a unit density sphere having the same settling velocity, generally in air, as the particle. The aerodynamic diameter encompasses particle shape, density and physical size of a particle. As used herein, MMAD refers to the midpoint or median of the aerodynamic particle size distribution of an aerosolized powder determined by cascade impaction.

[0058] In one version, the powdered or liquid formulation for use in the present invention includes an aerosol having a particle or droplet size selected to permit penetration into the alveoli of the lungs, that is, preferably 10 μm mass median diameter (MMD), preferably less than 7.5 μm, and most preferably less than 5 μm, and usually being in the range of 0.1 μm to 5 μm in diameter. When in a dry powder form, the pharmaceutical formulation may have a moisture content below about 10% by weight, usually below about 5% by weight, and preferably below about 3% by weight. Such powders are described in WO 95/24183, WO 96/32149, WO 99/16419, and WO 99/16422, all of which are all incorporated herein by reference in their entireties.

[0059] Although the present invention has been described in considerable detail with regard to certain preferred versions thereof, other versions are possible, and alterations, permutations and equivalents of the version shown will become apparent to those skilled in the art upon a reading of the specification and study of the drawings. For example, the relative positions of the elements in the aerosolization device may be changed, and flexible parts may be replaced by more rigid parts that are hinged, or otherwise movable, to mimic the action of the flexible part. In addition, the passageways need not necessarily be substantially linear, as shown in the drawings, but may be curved or angled, for example. Also, the various features of the versions herein can be combined in various ways to provide additional versions of the present invention. Furthermore, certain terminology has been used for the purposes of descriptive clarity, and not to limit the present invention. Therefore, any appended claims should not be limited to the description of the preferred versions contained herein and should include all such alterations, permutations, and equivalents as fall within the true spirit and scope of the present invention.

What is claimed is:

1. A pharmaceutical dry powder formulation comprising:

particles comprised of multiple active agents.

2. The formulation of claim 1 wherein the multiple active agents are antibiotics.

3. The formulation of claim 1 wherein the multiple active agents comprise a gram negative antibiotic and a gram positive antibiotic.

4. The formulation of claim 2 wherein the particle further comprises a flow enhancing agent.

5. The formulation of claim 4 wherein the flow enhancing agent comprises one or more of trileucine, an amino acid, a di-peptide, or a tri-peptide.

6. The formulation of claim 1 wherein the dry powder is respirable.

7. The formulation of claim 2 wherein the particle further comprises one or more pharmaceutical excipients which are suitable for pulmonary administration.

8. The formulation of claim 2 wherein the excipients comprise one or more of amino acids, peptides, proteins, non-biological polymers, biological polymers, and carbohydrates.

9. The formulation of claim 8 wherein the carbohydrates are sugars.

10. The formulation of claim 8 wherein the carbohydrates are derivatized sugars.

11. The formulation of claim 10 wherein the derivatized sugars are alditols, aldonic acids, or esterified sugars

12. The formulation of claim 8 wherein the carbohydrates are sugar polymers.

13. The formulation of claim 2 wherein the particle further comprises a pH adjusting agent.

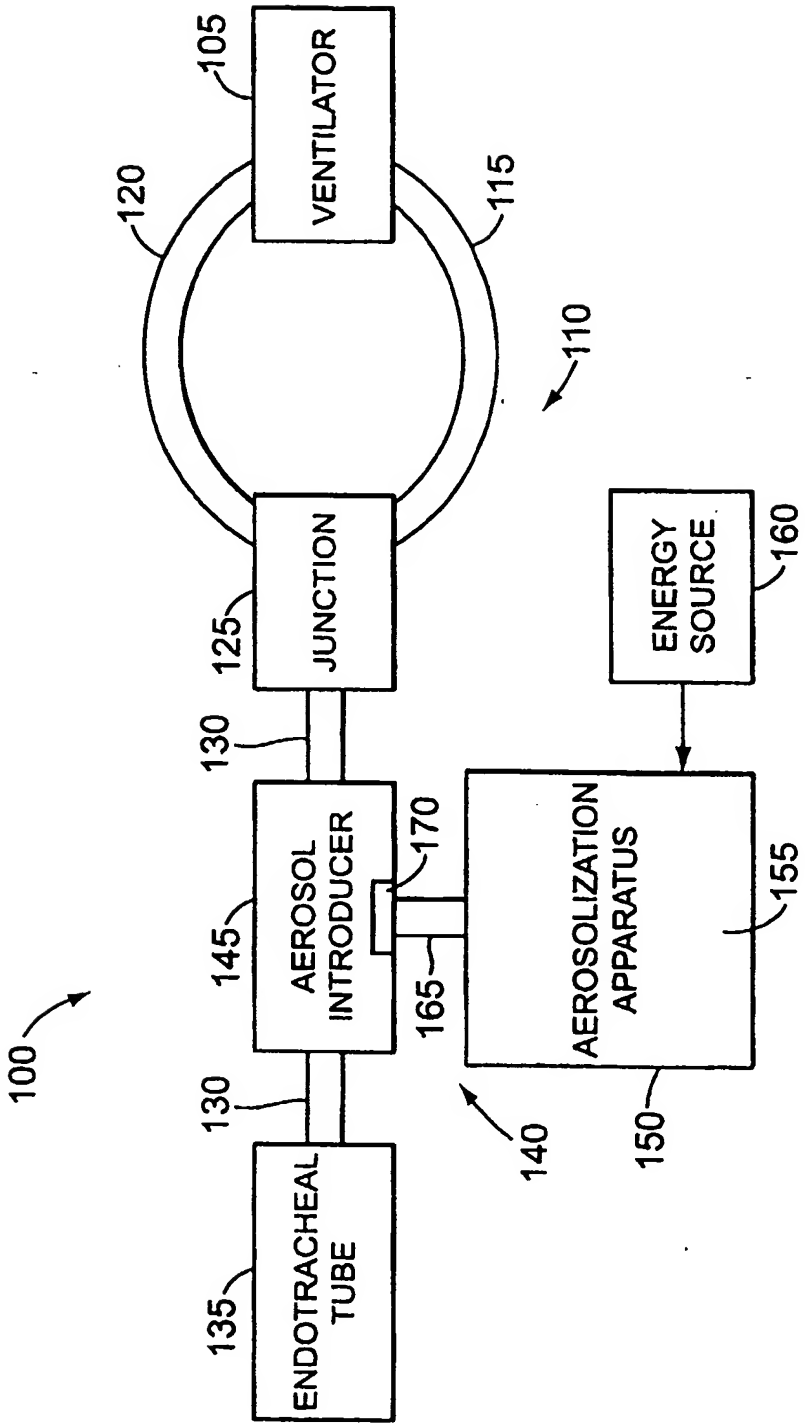
14. The formulation of claim 2 wherein the particle further comprises flavoring agents.

15. A pharmaceutical dry powder formulation comprising:

particles comprised of multiple active agents and having a moisture content less than about 10% by weight.

16. A pharmaceutical dry powder formulation comprising:

particles comprised of multiple active agents and having an MMAD less than 10 μm.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VENTILATOR
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125
JUNCTION
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145
AEROSOL INTRODUCER
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135
ENDOTRACHEAL TUBE
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150
AEROSOLIZATION APPARATUS
155
ENERGY SOURCE
160

FIG. 1

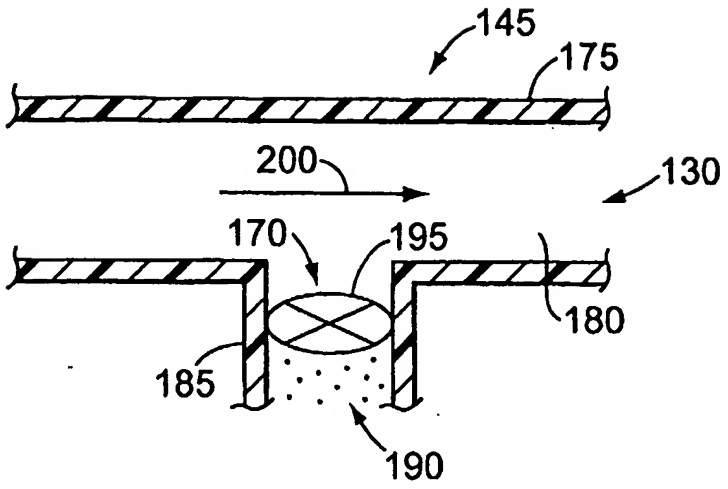
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FIG. 2A

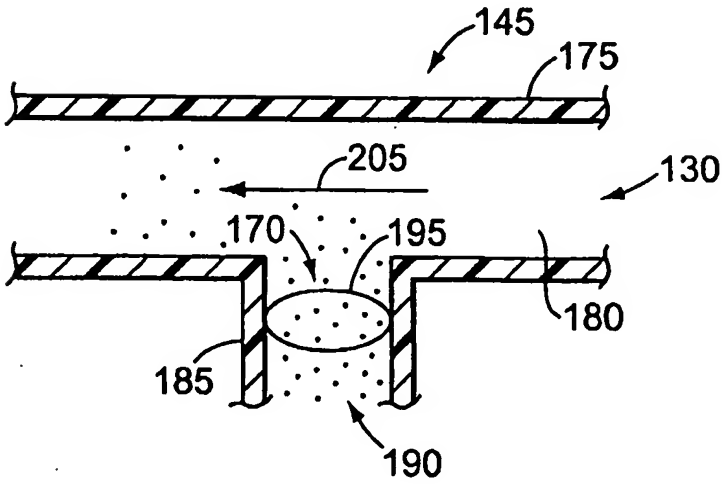
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FIG. 2B

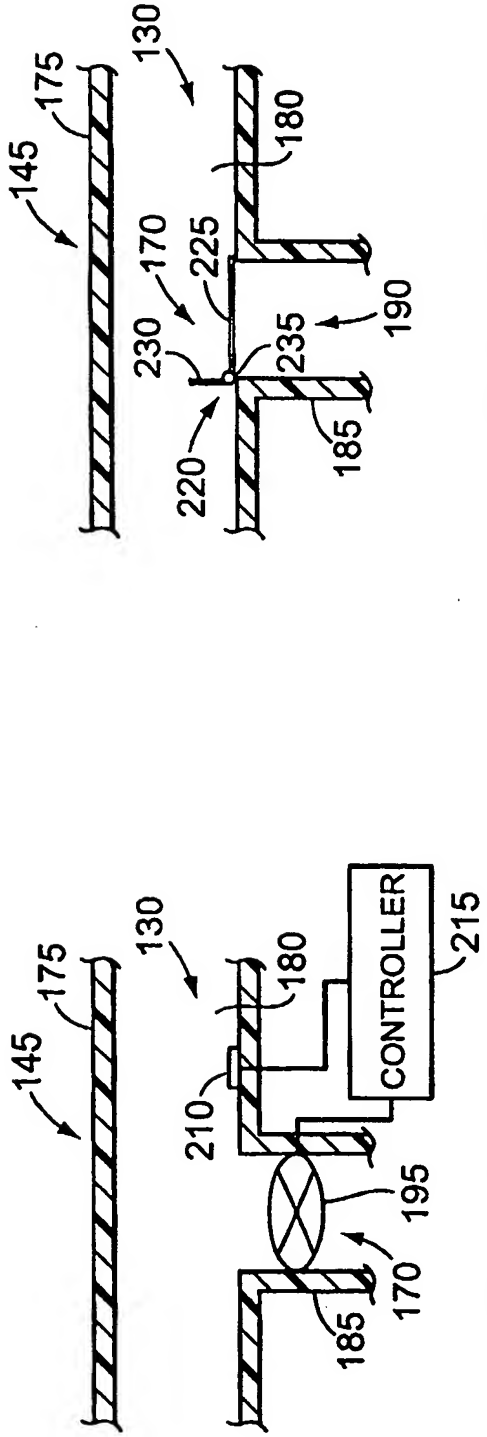

FIG. 3A

FIG. 3B

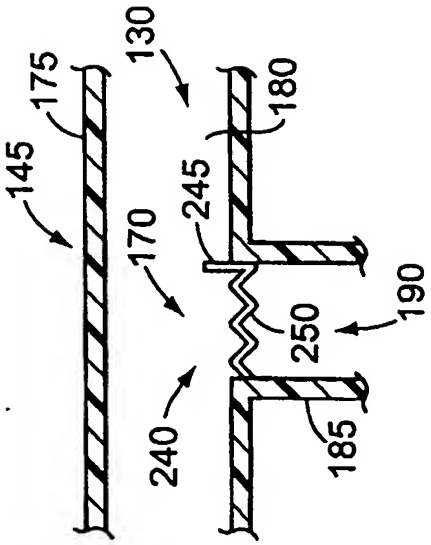

FIG. 3C

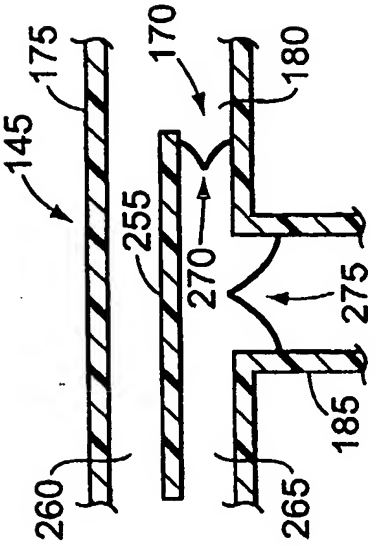

FIG. 4B

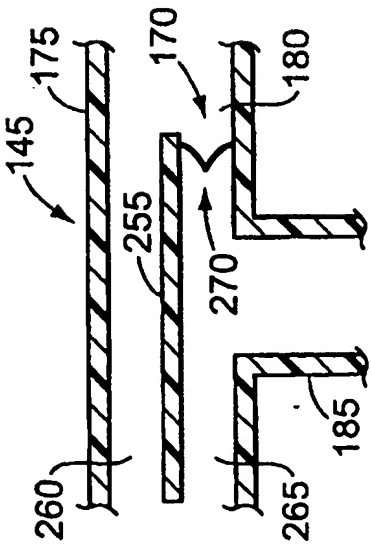

FIG. 4A

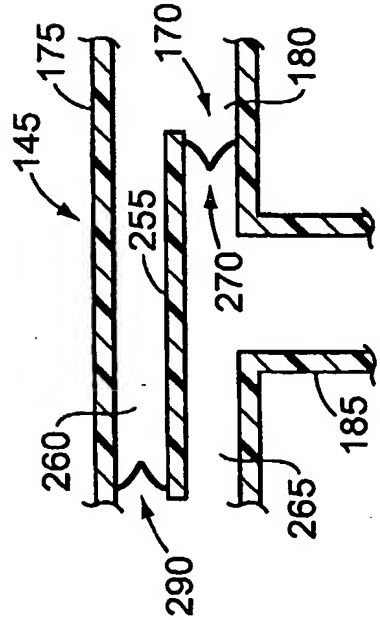

FIG. 4D

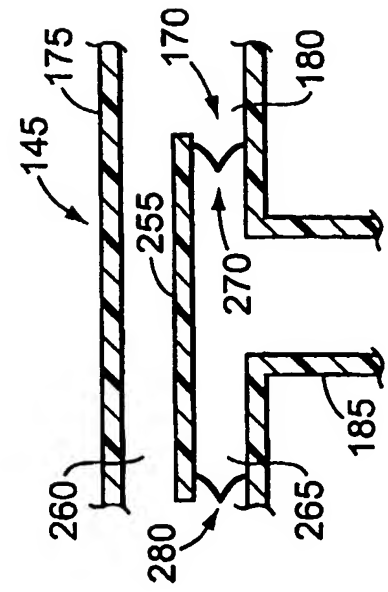

FIG. 4C

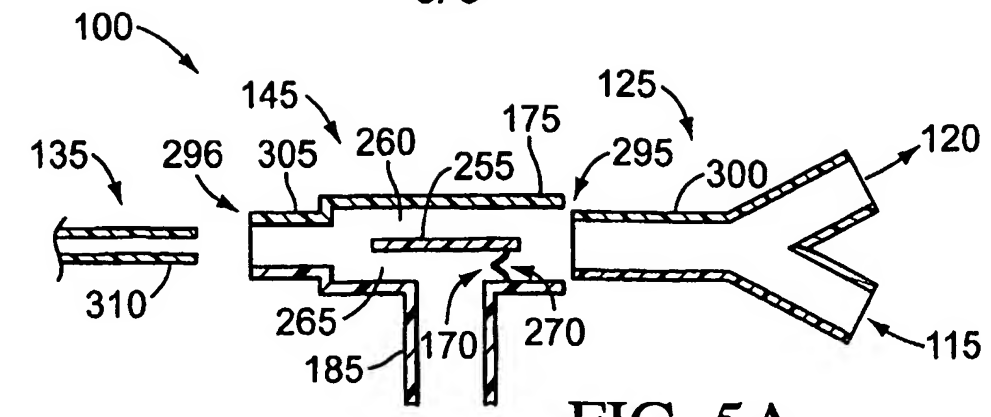

FIG. 5A

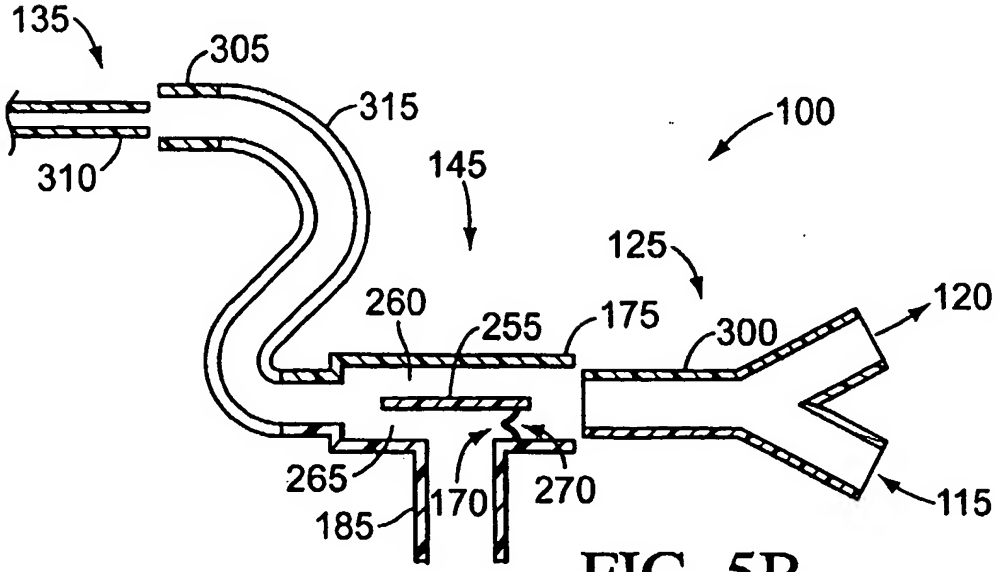

FIG. 5B

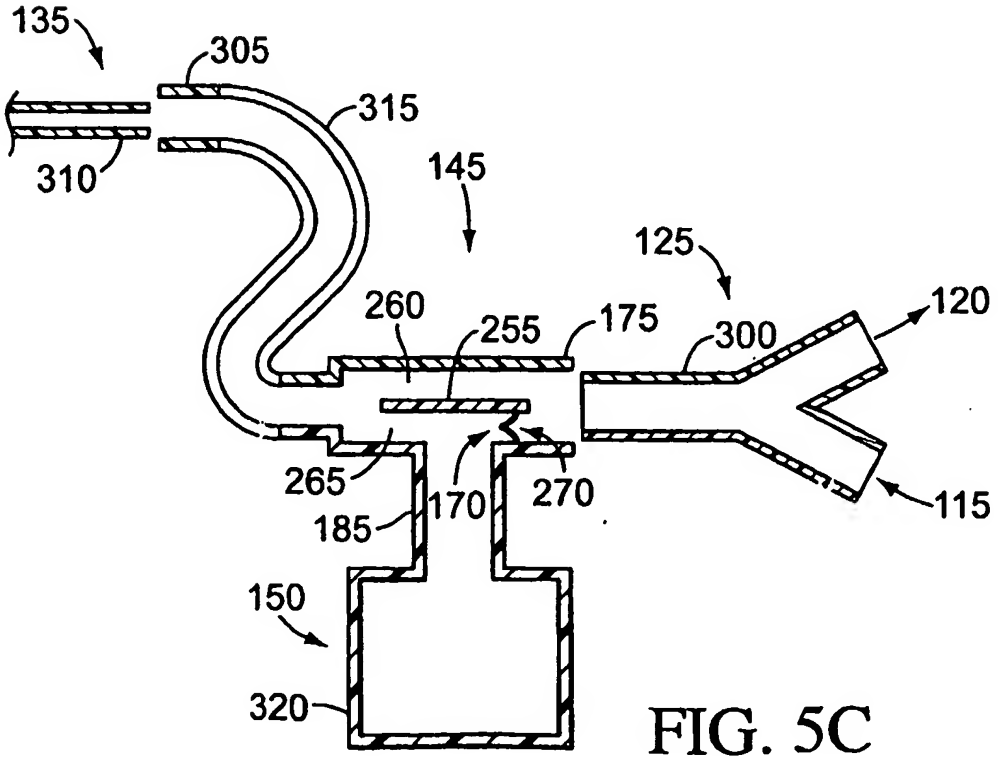

FIG. 5C

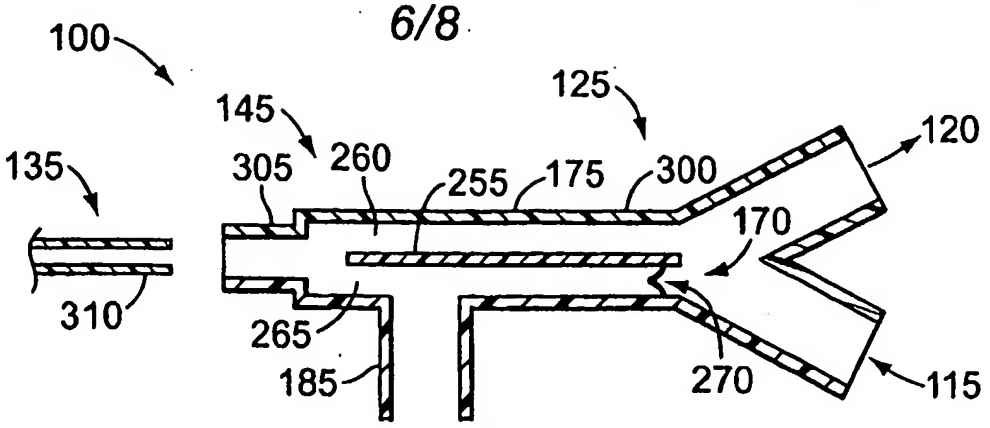

FIG. 6A

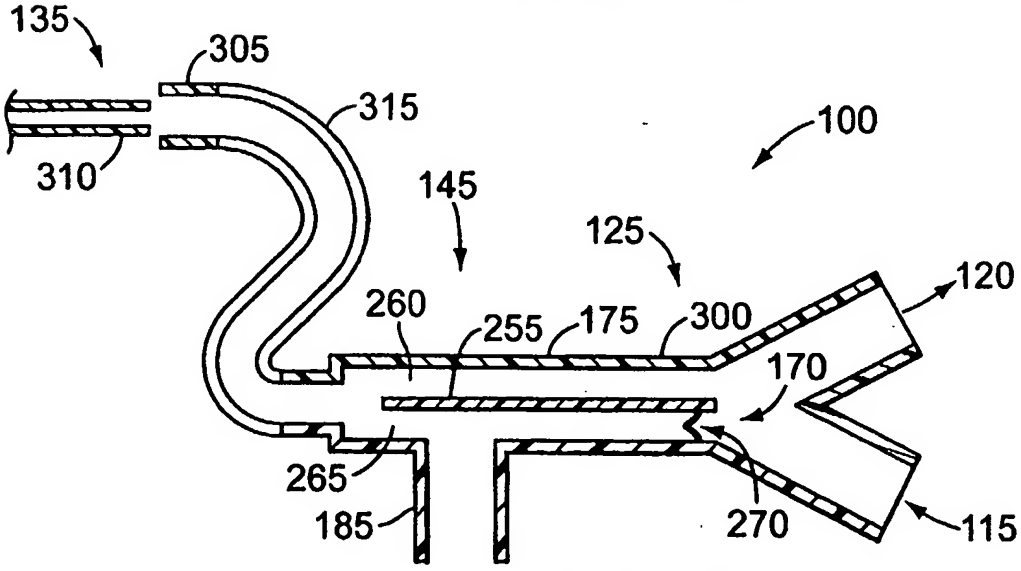

FIG. 6B

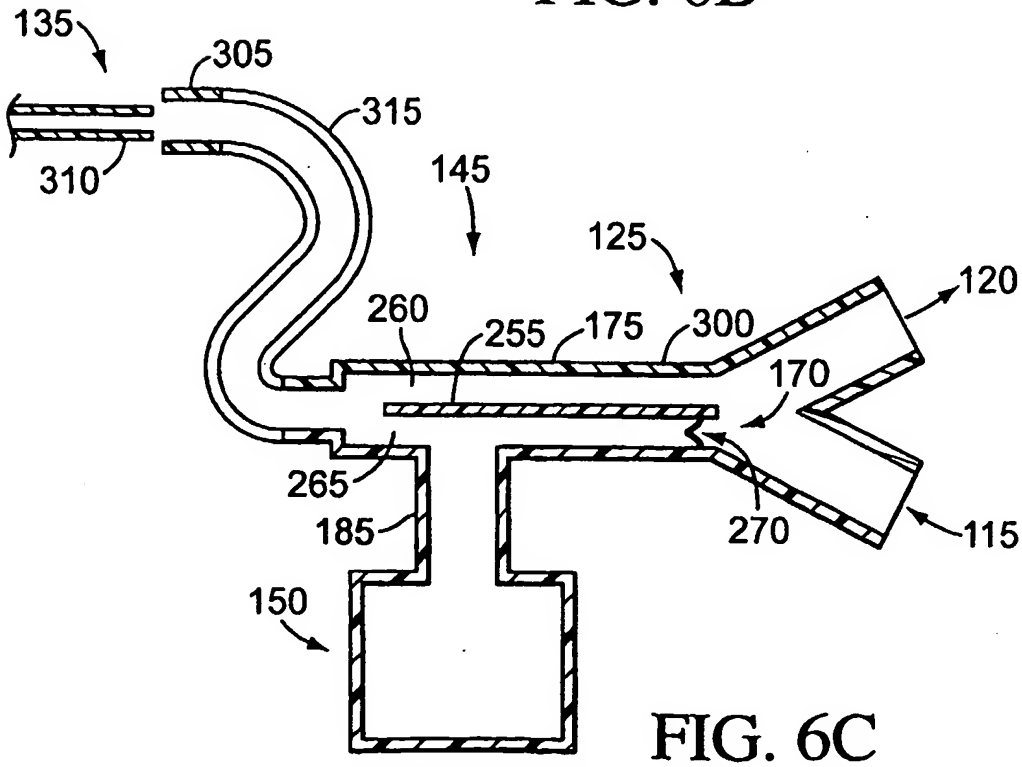

FIG. 6C

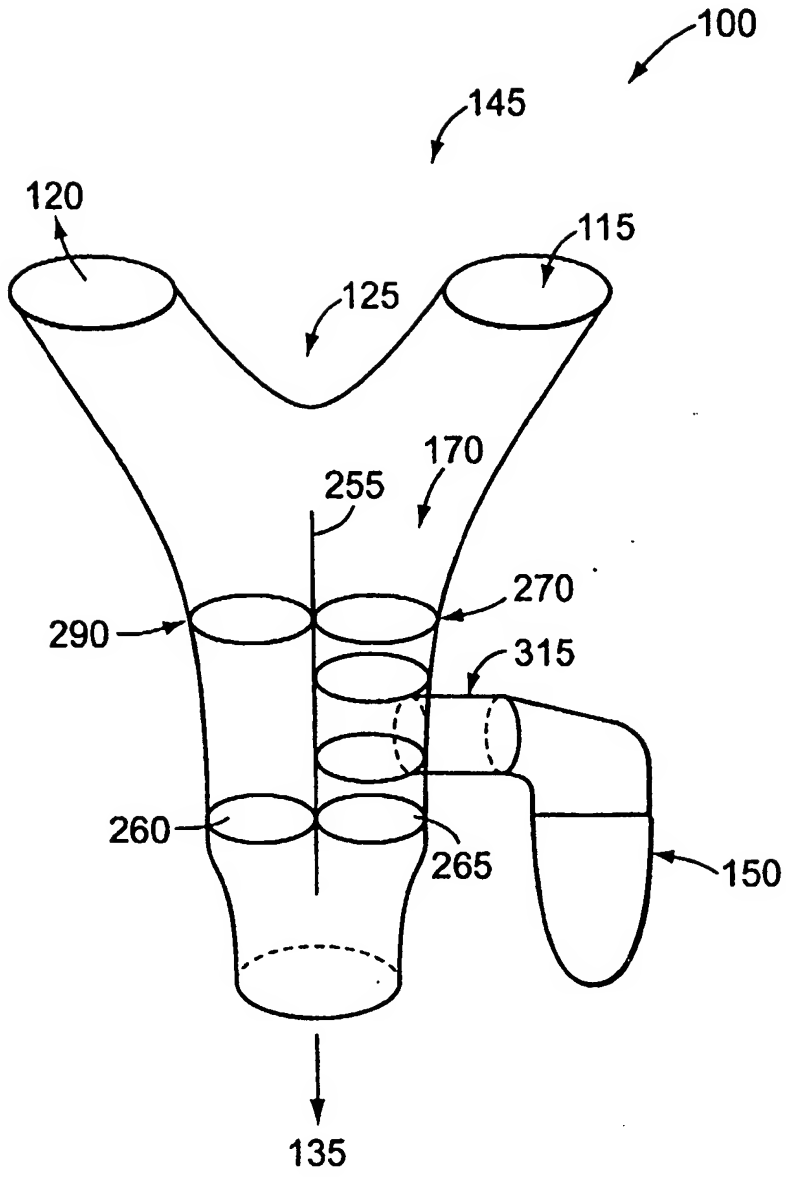

FIG. 7

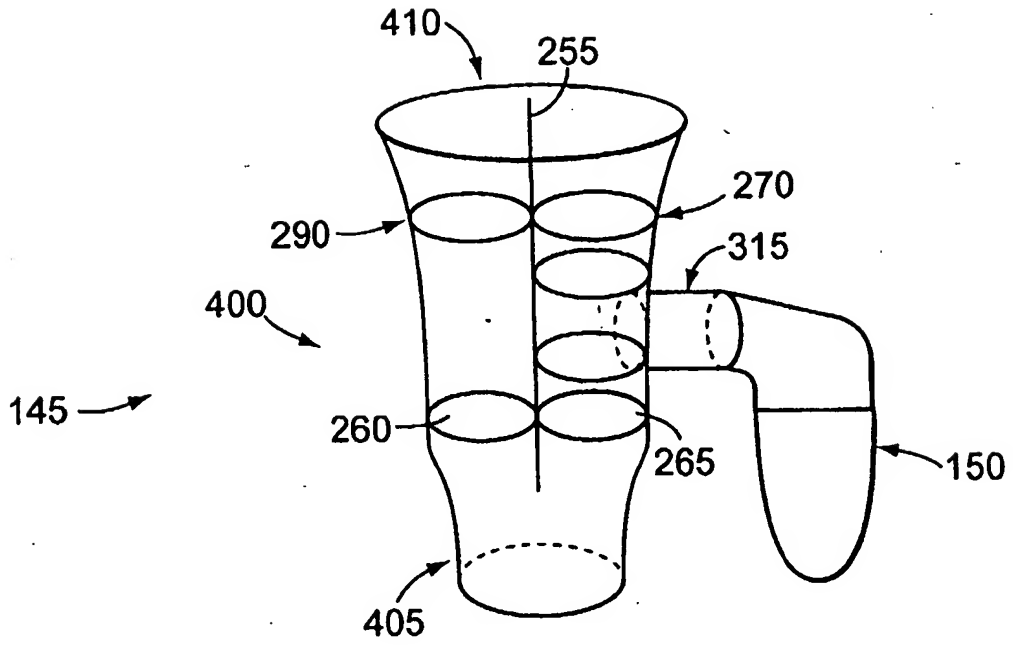

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/042277

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/12 A61K9/00 A61K9/14 A61P31/04 A61P31/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 071 497 A (STEINER ET AL) 6 June 2000 (2000-06-06) claims 1-6 column 8, line 50 - column 10, line 52	1,6,7, 13-16
X	US 6 153 224 A (STANIFORTH ET AL) 28 November 2000 (2000-11-28) claims 1-25	1,4-8, 13-16
X	WO 02/43705 A (UNIVERSITY OF FLORIDA) 6 June 2002 (2002-06-06) claims 1,2 page 4, line 15 - page 14, line 7	1,6-8, 13-16
X	US 2002/193730 A1 (DAUGHERTY ANN L) 19 December 2002 (2002-12-19) claims 1-11 paragraph [0019] - paragraph [0029]	1,2,6,7, 13-16

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
11 April 2006	27/04/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schifferer, H

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